Peroxisome Proliferator-Activated Receptor (PPAR) Agonists

Preclinical and Clinical Cardiac Safety Considerations

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PPAR Agonist Therapeutics

- PPAR gamma agonists - insulin sensitizers for type 2 diabetes
  - Approved drugs – Actos (pioglitazone), Avandia (rosiglitazone)

  PPAR alpha agonists –for dyslipidemia, increase HDL, decrease TG, no effects on LDL.
  Approved drugs – fibrates (fenofibrate, clofibrate)

  PPAR dual agonists (alpha/gamma) – being developed for combined treatment of type 2 diabetes and dyslipidemia
  Muraglitazar, Tesaglitazar, Ragaglitazar, Naveglitazar

  PPAR delta agonists – being developed for obesity

  PPAR pan agonists (alpha/delta/gamma) – being developed for type 2 diabetes and dyslipidemia

PPAR Agonist Development Chronology

- Troglitazone – approved 1997. Removed from market for safety concern (i.e., drug-induced liver failure) in 2000.
- Pioglitazone and Rosiglitazone – approved by FDA in 1999.
- Seven years since last approval despite intense interest in this therapeutic area, i.e., dozens of compounds in development (> 50 INDs).
- Numerous development programs terminated – all for safety issues.
- Toxicities observed in animals are also observed clinically . (e.g., cardiac, skeletal muscle, renal, bone marrow).

Most agonists in development are non-thiazolidinediones. Liver toxicity has not been a clinical safety issue.

Discontinuations for Clinical Cardiac Safety

- Indirect - PPAR gamma-mediated fluid accumulation, weight gain, and edema leading to excess CHF (dose and duration dependent, may be pharmacologic effect on kidney)
  - Approved drugs – re-labeled to describe CHF risk
  - Pro-active study – Pioglitazone (Lancet 366:9493, Oct. 2005)
  - Muraglitazar Advisory Committee - Sept. 2005
  - Numerous other non-approved drugs with clinical safety signal for excess edema/CHF (gamma and dual agonists).

Direct cardiotoxicity(?) – death, MI, stroke, TIA.

Clinical – Muraglitazar Advisory Committee, Sept 2005

Preclinical evidence for direct cardiotoxicity with dual and alpha agonists.

Discontinuations for Clinical Safety Non-cardiac

- Skeletal muscle toxicity – rhabdomyolysis in Phase 1 trials
  - Led to discontinuation of 1 dual , 1 alpha agonist

- Renal toxicity – > 50% increases in creatinine, excess renal failure
  - Led to discontinuation of 2 dual agonists.

Nonclinical Safety Issues : Rodent Carcinogenicity Findings

- **Drug- related increases in tumors with gamma and dual agonists**

  Mouse (CD-1, B6C3F1)
  hemangiosarcomas observed with 10/13 compounds

  Rat (SD, Wistar, Fischer) -
  - Bladder tumors – 5/7 dual agonists (negative in Wistar rats)
  - Sarcomatous tumors of adipose, skin, renal tubules, muscle (uterus, stomach)- more common with dual agonists

  - According to the International Agency for Research on Cancer (IARC) and Environmental Protection Agency (EPA) criteria :
  - Multi-species, multi-strain, multi-sex, multi-site carcinogens = "probable human carcinogen"

  Class-related tumor findings led to development of policy requiring completion of rodent carcinogenicity studies prior to the initiation of Phase 3 clinical studies (> 6 months duration).

Discontinuation for Nonclinical Safety Issues

- Five dual agonists discontinued (by sponsors) for multi-species, multi-sex, multi-site increases in tumors with no safety margins for clinical exposures.

  Three compounds terminated prior to CDER recommendations for completion of carcinogenicity testing prior to Phase 3. (June 2004).

  Development of 2 additional compounds terminated for rodent carcinogenicity findings (multispecies, multisite tumors at all doses) since the CDER policy was implemented.

- Brain lesions – not monitorable or reversible
  ventricular dilation, brain vacuolation –dog (n = 1 drug)
  brain hemorrhages – monkey (n = 1 drug)

PPAR Safety Summary

- PPAR gamma-mediated fluid accumulation, edema, weight gain with consequent increased frequency of CHF is the major dose-limiting adverse event.
- The fluid accumulation and resultant adverse cardiac effects are observed preclinically and clinically with virtually all compounds with PPAR gamma activity (gamma, dual , and pan agonists).
- Clinical safety issues responsible for the discontinuation of more compounds than rodent carcinogenicity issues.

While the approved drugs are associated with increased edema and CHF, there is no evidence of direct cardiotoxicity with the approved PPAR gamma agonists.

PPAR Gamma-Mediated Cardiac Toxicity

- Fluid accumulation in all species (mouse, rat, dog, rabbit, monkey, human).
- Fluid accumulation leads to weight gain, edema, cardiac hypertrophy with resultant heart failure in all species.
- Dogs more sensitive to PPAR toxic effects than other species, thus not helpful for establishing safety margins for clinical doses. Led to recommendation that general toxicity testing be conducted in rats and monkeys.
- Fluid accumulation, weight gain, cardiac hypertrophy observed with short latency (within 1-3 months).
- Drug-induced heart failure and death observed with chronic treatment (> 6 months in animals and man).
  - Led to recommendation for 1 year non-rodent toxicity study in attempt to define NOAEL exposures for chronic clinical dosing.

PPAR-Related Cardiac Toxicity: Nonclinical

- Atrial thrombi, pericardial/thoracic effusions, cardiomyopathy, interstitial expansion, and CHF-related deaths observed in rats and monkeys with chronic treatment (1 yr in monkey, > 1 year in rats and mice).
- Dual and alpha agonists also associated with direct cardiomyopathy in mice, rats, dogs, and monkeys.
- No adverse effect levels (NOAEL) for fluid accumulation and resultant adverse cardiac effects (CHF, death) decrease markedly with increased treatment duration in animals and humans.
  - Safe doses in Phase 2 clinical trials do not predict safe doses for Phase 3 or chronic treatment.
- Division defines NOAELs for cardiac toxicity using data from the longest duration nonclinical studies (1 yr monkey, 2 year rat). Therefore, data from rodent carcinogenicity studies used to determine NOAELs for cardiac safety, as well as safety margins for carcinogencity.

Endocrinologic and Metabolic Drugs

Effect of Treatment Duration on LOAEL Clinical Examples

Duration	12 -16 Wks	24-26 Wks	52 Wks	
Gamma				
Edema	20 mg	10 mg	2.5 mg	
CHF	-------	10 mg	5 mg	
Gamma				
Edema	20 mg	5 mg	No data	
CHF	--------	10 mg	No data	
Dual				
Edema	20 mg	5 mg	2.5 mg	
CHF	---------	10 mg	5 mg	
Dual				
Edema	5 mg	2 mg	0.5 mg	
CHF	-------	--------	1 mg	

Implications of Cardiac Toxicity for Carcinogenicity Testing

- Doses which increase heart weights ≥ 25% in rodents at 3 months result in premature cardiac mortality in 2- year carcinogenicity studies.
- Rats more sensitive to developing failure secondary to fluid accumulation and cardiac hypertrophy than mice.
- 20-25% increases in heart weight accepted to establish the maximum tolerated dose (MTD) for carcinogenicity testing in both rodent species.
- This paradigm developed based on experience with PPAR gamma agonists and successfully predicts MTD for most gamma only compounds .
- However, use of 20-25% increase in heart wt to define the high dose (MTD) for dual agonists has been less successful. Premature mortality still observed with high dose in 2 year rat studies with most dual agonists . Data suggest addition of alpha activity to dual agonist enhances cardiac toxicity .

Implications of Cardiac Toxicity for Clinical Study Design

- Patients with NYHA class 3 and 4 cardiac disease have usually been excluded from Phase 3 trials.
- Phase 2 and 3 protocols should include prospective monitoring for fluid accumulation, weight gain, edema
- Stopping criteria should be predefined.
- Monitor diuretics use or dose changes.
- DSMB adjudication of cardiac morbidity and mortality (e.g., CHF, MI, stroke, TIA, death).

Implications of Cardiac Toxicity for Clinical Studies (slide 1)

- Phase 3 studies should be designed as one year controlled trials with collection of open label safety data for up to 2 years in a significant number of patients (e.g., minimum of 500 subjects for 18 months and 200 for 2 years).

- Phase 3 dose selections based on drug exposures at NOAELs in the chronic preclinical studies and Phase 2 safety data have been associated with excess cardiac toxicity (edema, heart failure and cardiac morbidity) in numerous failed Phase 3 programs.

- Phase 3 trials only justified if safety margin is fully adequate at doses expected to have sufficient clinical effect
- (i.e, if edema is observed at doses close to those required for efficacy, drug may not be a good candidate for further development).

Implications of Cardiac Toxicity for Clinical Studies (slide 2)

- Phase 3 clinical safety data suggest that humans with type 2 diabetes are more sensitive to the chronic cardiotoxic effects of PPAR agonists than the young healthy animals used in preclinical toxicology studies. (i.e., drug exposures at NOAELs in rodents and monkeys over estimate safety margins).

- Cardiac toxicity is progressive in humans and animals . (i.e., seen at lower doses/AUC exposures with longer treatment duration).

  Doses without cardiac safety signals after chronic treatment are usually 5 to 10- fold lower than doses considered safe after 12-16 weeks of treatment.

Recommendations for Phase 3 Study Designs

- Evaluation of cardiac safety data from chronic preclinical studies and Phase 2 clinical studies will be conducted prior to the initiation of Phase 3 trials. (coincident with the submission of the rodent carcinogenicity data).
- Cardiac safety assessment may result in dose limitations and/or the recommendation for collection of cardiac outcomes data in Phase 3 trials .
- Currently, recommendations for Phase 3 cardiac outcome studies will be made on a case-by -case basis dependent on the cardiac safety profile of each compound.